Ex. 7

# EXHIBIT 7

# NDA SUBMISSION LETTER

**PARKE-DAVIS**
Pharmaceutical Research Division
Warner-Lambert Company


December 27, 1990

NDA 20-130
Ref. No. 1
Estrostep® (norethindrone and ethinyl estradiol, USP) Tablets

Re: Original New Drug Application

Food and Drug Administration
Document and Records Section
12420 Parklawn Drive
Rockville, Maryland 20852

Dear Sir/Madam:

Enclosed is a New Drug Application for Estrostep® (norethindrone acetate and ethinyl estradiol, USP) Tablets for oral contraception. Estrostep will be provided in a 21- or 28-day package, for dosing starting with 5 days of a triangular, white tablet containing 1 mg of norethindrone acetate (NA) and 20 μg of ethinyl estradiol (EE), then 7 days of a square, white tablet containing 1 mg NA and 30 μg of EE, followed by 9 days of a round, white tablet containing 1 mg NA and 35 μg of EE. The 28-day package will also contain 7 round, brown tablets containing 75 mg ferrous fumarate, USP.

Estrostep is a graduated-estrogen-dose oral contraceptive. The unique dosage formulation of ethinyl estradiol and norethindrone acetate is designed to provide a gradually increasing amount of estrogen to the developing endometrium while maintaining low total monthly exposure to these steroids without compromising cycle control.

This NDA contains the results of study 376-364, a clinical study which meets the FDA guideline of 600 women for 6 cycles for a new oral contraceptive product containing previously approved drug substances.

Parke-Davis has met with the agency on numerous occasions to discuss the development of Estrostep (e.g., July 20, September 15, October 24, 1989). Please note that this NDA is for tablets of the same composition and manufactured by the same process as the clinical tablets. Results of bioavailability studies of tablets used in the efficacy trials are contained in the NDA. Since the tablets to be marketed are of the same composition and will be manufactured using the same process as the clinical tablets, bioequivalence studies of these clinical and commercial tablets are not appropriate.

Estrostep has been investigated by Parke-Davis under IND 31,861. Please also refer to NDA 13-554 for Norlestrin® and NDA 17-876 for Loestrin® for information on Nonclinical Pharmacology and Toxicology (NDA Item 5) for the active drug substances in Estrostep (norethindrone acetate and ethinyl estradiol).

The patent and exclusivity information required by 21 U.S.C. 355 (b)(1) is provided in this volume as Item 13.

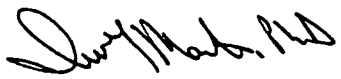
Four copies of the Methods Validation Package are contained with this NDA: one copy with the archival copy and three with the Chemistry, Manufacturing and Controls review copy. Draft copies of the physician package insert are contained in the archival copy and each of the technical review copies in Volume 1.

Parke-Davis will test the stability of at least the first three commercial lots of each strength of tablet according to the commercial stability testing protocol provided in Item 3, Chemistry, Manufacturing and Controls, of this application. Please also refer to the discussion between Dr. Yuan Yuan Chiu of the Division of Metabolism and Endocrine Drug Products and Dr. Sean Brennan of our staff on October 26, 1990. During this meeting it was agreed that 3-month stability data on the full scale lots could be submitted to this NDA during the 60-day window between submission and filing. We hereby make such a commitment as well as agree to update stability data obtained via the developmental stability protocol described in Item 3 of this NDA through additional NDA amendments. Additionally, draft copies of the typeset package and container labels will be provided in the first amendment to this NDA.

Estrostep has not been submitted for registration in any other country.

During your review of this application, please contact the undersigned at (313) 996-7756 for any questions pertaining to this NDA.

Sincerely yours,



Irwin G. Martin, Ph.D.
Director
Worldwide Regulatory Affairs

IGM/ma121890

Attachments

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

# APPLICATION TO MARKET A NEW DRUG FOR HUMAN USE OR AN ANTIBIOTIC DRUG FOR HUMAN USE

*(Title 21, Code of Federal Regulations, 314)*

Form Approved OMB No 0910-0001
Expiration Date, November 30, 1990
See OMB Statement on Page 3.

FOR FDA USE ONLY

| DATE RECEIVED | DATE FILED |
|---|---|
| | |
| DIVISION ASSIGNED | NDA/ANDA NO. ASS. |
| | |

NOTE: No application may be filed unless a completed application form has been received (21 CFR Part 314).

NAME OF APPLICANT
Parke-Davis Research Division of Warner-Lambert Co.

DATE OF SUBMISSION
December 27, 1990

TELEPHONE NO (Include Area Code)
(313) 996-7000

ADDRESS (Number, Street, City, State and Zip Code)
2800 Plymouth Rd.
Ann Arbor, MI 48105

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER (If previously issued)
20-130

## DRUG PRODUCT

ESTABLISHED NAME (e.g., USP/USAN)
Norethindrone Acetate and Ethinyl Estradiol

PROPRIETARY NAME (If any)
Estrostep 21
Estrostep Fe

CODE NAME (If any)
CI-376

CHEMICAL NAME
(17α)-19-Norpregna-1,3,5 (10)-trien-20-yne-3,17-diol and (17α)-17-(acetyloxy)-19-norpregn-4-en-20-yn-3-one

DOSAGE FORM
Tablets

ROUTE OF ADMINISTRATION
Oral

STRENGTH(S)
1mg/20µg
1mg/30µg
1mg/35µg

PROPOSED INDICATIONS FOR USE

Contraceptive

LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS (21 CFR Part 312), NEW DRUG OR ANTIBIOTIC APPLICATIONS (21 CFR Part 314), AND DRUG MASTER FILES (21 CFR 314.420) REFERRED TO IN THIS APPLICATION:

IND 31,861
NDA 17-875
NDA 17-876
NDA 16-746
NDA 16-852
NDA 17-354
NDA 17-355
NDA 16-766
NDA 16-854
NDA 13-554
see attached for DMF numbers

CENTER FOR ... REC'D DEC 28 CDR EVALUATION AND RESEARCH

## INFORMATION ON APPLICATION

TYPE OF APPLICATION (Check one)

☒ THIS SUBMISSION IS A FULL APPLICATION (21 CFR 314.50) ☐ THIS SUBMISSION IS AN ABBREVIATED APPLICATION (ANDA) (21 CFR 314.55)

IF AN ANDA, IDENTIFY THE APPROVED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

| NAME OF DRUG | HOLDER OF APPROVED APPLICATION |
|---|---|
| | |

STATUS OF APPLICATION (Check one)

☐ PRESUBMISSION ☒ ORIGINAL APPLICATION ☐ AN AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION ☐ SUPPLEMENTAL APPLICATION

PROPOSED MARKETING STATUS (Check one)

☒ APPLICATION FOR A PRESCRIPTION DRUG PRODUCT (Rx) ☐ APPLICATION FOR AN OVER-THE-COUNTER PRODUCT (OTC)

| CONTENTS OF APPLICATION | |
|---|---|
| This application contains the following items: *(Check all that apply)* | |
| X | 1. Index |
| X | 2. Summary (21 CFR 314.50 (c)) |
| X | 3. Chemistry, manufacturing, and control section (21 CFR 314.50 (d) (1)) |
| | 4. a. Samples (21 CFR 314.50 (e) (1)) (Submit only upon FDA's request) |
| X | b. Methods Validation Package (21 CFR 314.50 (e) (2) (i)) |
| | c. Labeling (21 CFR 314.50 (e) (2) (ii)) |
| X | i. draft labeling *(4 copies)* |
| | ii. final printed labeling (12 copies) |
| | 5. Nonclinical pharmacology and toxicology section (21 CFR 314.50 (d) (2)) |
| X | 6. Human pharmacokinetics and bioavailability section (21 CFR 314.50 (d) (3)) |
| | 7. Microbiology section (21 CFR 314.50 (d) (4)) |
| X | 8. Clinical data section (21 CFR 314.50 (d) (5)) |
| | 9. Safety update report (21 CFR 314.50 (d) (5) (vi) (b)) |
| X | 10. Statistical section (21 CFR 314.50 (d) (6)) |
| X | 11. Case report tabulations (21 CFR 314.50 (f) (1)) |
| X | 12. Case reports forms (21 CFR 314.50 (f) (1)) |
| X | 13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c)) |
| | 14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A)) |
| | 15. OTHER *(Specify)* |

I agree to update this application with new safety information about the drug that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit these safety update reports as follows: (1) 4 months after the initial submission, (2) following receipt of an approvable letter and (3) at other times as requested by FDA. If this application is approved, I agree to comply with all laws and regulations that apply to approved applications, including the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211
2. Labeling regulations in 21 CFR 201.
3. In the case of a prescription drug product, prescription drug advertising regulations in 21 CFR 202
4. Regulations on making changes in application in 21 CFR 314.70, 314.71, and 314.72
5. Regulations on reports in 21 CFR 314.80 and 314.81.
6. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the controlled substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision

| NAME OF RESPONSIBLE OFFICIAL OR AGENT | SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT | DATE |
|---|---|---|
| Irwin G. Martin, Ph.D.<br>Director, Worldwide Regulatory Affairs | | |

| ADDRESS *(Street, City, State, Zip Code)* | TELEPHONE NO *(Include Area Code)* |
|---|---|
| 2800 Plymouth Rd.<br>Ann Arbor, MI 48105 | (313) 996-7756 |

(WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec.1001.)